REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed.

The May 3, 2004, personal interview between Examiner Ponnaluri, SPRE Tsang, and applicants' representatives, Michael Goldman and Jerome Massie, is gratefully acknowledged. The substance of the interview is summarized below.

Reconsideration of the written restriction requirement is respectfully traversed. As set forth in the Request for Declaration of Interference Under 37 CFR § 1.607(a), the Showing by Applicant Under 37 CFR § 1.608(b), and the accompanying declarations, filed on January 7, 2002, the present application was filed for the purpose of provoking an interference with U.S. Patent No. 6,156,501 to McGall, et. al., ("McGall '501"). In their current form, the claims of the present application are identical or virtually identical to those that issued together in McGall '501. Since such claims were not caused to be prosecuted and issued separately in McGall '501, they should not be prosecuted separately in the present application. Examining claims 1-37 together in the present application is not only most fair to applicants by obviating the need to prosecute multiple patent applications on that claimed subject matter, it also furthers the public interest. In particular, neither the U.S. Patent and Trademark Office ("PTO") nor the public benefits from the burden of having several patent applications to allowable subject matter separately examined and herded into interference with a single patent by itself containing all corresponding claims. Having previously decided in the case of McGall '501 that such claims should be examined and issued together, that decision should be adhered here to by withdrawing the restriction requirement and examining all of claims 1-37 together in this case.

The objection to the disclosure, because the bottom of pages 48, 49, and 52 are not clearly visible is respectfully traversed in view of applicants' submission of copies of those pages.

The rejection of claims 15-24 under 35 U.S.C. § 112 (2nd para.) is respectfully traversed in view of the above amendments, except as noted below in the following remarks.

Firstly, the limitations which form the basis for this ground of rejection are all found in the claims of McGall '501. In deciding to issue claims with such limitations in McGall '501, the PTO implicitly decided that those limitations satisfied the requirements of 35 U.S.C § 112 (2nd para.). Having made that decision in McGall '501, it is improper to

come to a different decision here. For this reason alone the indefinitenss rejections should be withdrawn.

With regard to claim 15, applicants submit that the phrase "oligonucleotide analogue array" is readily understandable to those skilled in the art. In particular, this phrase refers to an array containing capture oligonucleotides made from nucleotide analogues. The concept of an array of oligonucleotides is discussed throughout the present application, including at page 7, lines 21-27 and at page 11, lines 35-37. The use of nucleotide analogues to form the capture oligonucleotides on the array is also fully described in the present application. In particular, see e.g., page 8, lines 12-15, page 30, lines 32-34, and page 40, lines 35-37 of the present application. Since one of ordinary skill in the art would fully understand the phrase "oliogonucleotide analogue array" from the disclosure of the present application, the rejection based on any alleged indefiniteness of this phrase should be withdrawn.

The "similar hybridization stability across the array" limitation in claim 15 is also readily understandable to those skilled in the art. The present application notes that when attempting to detect multiple mutations simultaneously, it becomes difficult or impossible to optimize conditions to achieve such detection by simultaneous hybridization. See page 49, lines 15-16 of the present application. A method for high specificity detection of a correct signal, independent of the target sequence and under uniform hybridization conditions is disclosed at page 49, lines 16-18. Oligonucleotide capture can be optimized by narrowing the thermal stability (T_m) difference between duplexes formed by capture oligonucleotides and the complementary addressable array-specific portions hybridized to one another; this T_m difference results from differences in G·C/A·T content. See page 35, lines 12-15 of the present application. Since one of ordinary skill in the art would fully understand what is meant by the "similar hybridization stability across the array" limitation, that limitation forms no basis for an indefiniteness rejection.

With regard to claim 16, it is submitted that no essential elements are missing from the claims. The present invention is directed to an array of oligonucleotide analogue probes having similar hybridization stability across the array. There is no basis for limiting applicants to the use of a single specific oligonucleotide analogue (i.e. phosphoramidite derivative 5-propynyl-dU). Further, when the PTO issued McGall '501, it implicitly recognized that claims of the same breadth as claim 16 satisfy the provisions of 35 U.S.C. § 112 (2nd para.). There is no reason to deviate from that decision here.

For all of the above reasons, the rejection under 35 U.S.C. § 112 (2nd para.) should be withdrawn.

The rejection of claims 15 and 19-23 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,412,087 to McGall ("McGall '087") is respectfully traversed.

McGall '087 discloses the spacially-addressable immobilization of oligonucleotides and other biological polymers, such as proteins, on surfaces. There is no disclosure in McGall '087 of an oligonucleotide analogue array comprising a plurality of oligonucleotide analogue probes where the plurality of oligonucleotide analogue probes bind to complementary target nucleic acids with similar hybridization across the array.

Since McGall '087 fails to teach these aspects of the claimed invention, the rejection based on this reference should be withdrawn.

The rejection of claims 15, 22, and 24 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,723,320 to Dehlinger et. al., ("Dehlinger") is respectfully traversed.

Dehlinger discloses a method of producing a high density, position-addressable gene array, employing an array of oligonucleotides with different sequences. There is no disclosure in Dehlinger of an oligonucleotide analogue array comprising a plurality of oligonucleotide analogue probes where the plurality of oligonucleotide analogue probes bind to complementary target nucleic acids with similar hybridization across the array.

Since Dehlinger fails to teach these aspects of the claimed invention, the rejection based on this reference should be withdrawn.

The rejection of claims 15-24 under 35 U.S.C. § 102(e) as anticipated by McGall '501 is respectfully traversed.

As set forth in the Request for Declaration of Interference Under 37 CFR § 1.607(a), the Showing by Applicant Under 37 CFR § 1.608(b), and the accompanying declarations, filed on January 7, 2002, applicants are seeking to provoke an interference with McGall '501 based on applicants having a date of invention preceding the effective filing date of McGall. Under these circumstances and where the claims of McGall '501 are the same or substantially the same as those pending before the PTO in the present application, it is entirely inappropriate for a rejection under 35 U.S.C. § 102(e) to be made. For all of these reasons, the rejections based on McGall '501 should be withdrawn.

The rejection of claims 15, 17-18, 20-22, and 24 under 35 U.S.C. § 103 for obviousness U.S. Patent No. 5,700,637 to Southern ("Southern") and U.S. Patent No. 5,594,121 to Froehler, et. al., ("Froehler") is respectfully traversed.

Southern discloses an apparatus and a method for analyzing polynucleotide sequences as well as a method of generating oligonucleotide arrays. The oligonucleotides forming the array are only disclosed to be formed from conventional nucleotides. Thus, Southern fails to disclose an oligonucleotide analogue array comprising a plurality of oligonucleotide analogue probes where the plurality of oligonucleotide analogue probes bind to complementary target nucleic acids with similar hybridization across the array, as claimed.

Froehler discloses oligomers containing 7-deaza-7-substituted purines or related analogs. However, Froehler fails to disclose an oligonucleotide analogue array comprising a plurality of oligonucleotide analogue probes where the plurality of oligonucleotide analogue probes bind to complementary target nucleic acids with similar hybridization across the array, as claimed.

Since both Southern and Froehler fail to teach an important claim limitation, their combination cannot be properly used to reject the claimed invention. Accordingly, the obviousness rejection based on the combination of these references should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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which both halves can independently rotate. The bottom portion 114B is a cylindrical block with 6 channels 130 drilled through it (see Figure 26C, which is a bottom view of Figure 26B taken along line 26C-26C of Figure 26B). Each of the 6 channels 130 are attached to 6 different input tubes 110. The input tubes 110 contain valves 106 which connect the input channels 130 to either reagents, solvent, or a vacuum via lines 138 having valves 136 leading to vacuum line 112 having valve 108 and solvent line 122 having valve 124. This allows different fluids to enter the channels 130 and 132 of the manifold and allows clearing of the channels 130 and 132 of excess fluid between fluid transfers. The upper portion of the manifold (see Figure 26A, which is a top view of Figure 26B taken along line 26A-26A of Figure 26B) is also a cylindrical block with 5 channels 132 drilled through it. The 5 channels 132 are each connected to a different output tube 116. The two halves of manifold 114A and 114B can be independently rotated so that different input channels 130 will line up with different output channels 132. This allows the 6 tubes of input fluids to be transferred to the 5 output tubes simultaneously. The bottom half of the manifold 114B can be rotated 60 degrees in order to align each input port 110 with the next output port 116. In this way, each input port 110 can be aligned with any of the output ports 116. The circular manifold of Figures 26A-D differs from the valve block assembly of Figures 26A-C in that the former can simultaneously transfer five of the six input fluids to the five output ports, because it has 5 channels connecting input ports to the output ports. This concept could be easily expanded to deliver 36 tetramers simultaneously to 36 locations.

The present invention contains a number of advantages over prior art systems.

The solid support containing DNA arrays, in accordance with the present invention, detects sequences by hybridization of ligated product sequences to specific locations on the array so that the position of the signal emanating from captured labels identifies the presence of the sequence. For high throughput detection of specific multiplexed LDR products, addressable array-specific portions guide each LDR product to a designated address on the solid support. While other DNA chip approaches try to distinguish closely related sequences by subtle differences in melting temperatures during solution-to-surface hybridization, the present invention achieves the required specificity prior to hybridization in solution-based LDR reactions. Thus, the present invention allows for the design of arrays of capture oligonucleotides with sequences which are very different from each other. Each LDR product will have a unique addressable array-specific portion, which is captured selectively by a capture oligonucleotide at a specific address on the solid support. When the complementary capture oligonucleotides on the solid support are either modified DNA or PNA, LDR products can be captured at higher temperatures. This provides the added advantages of shorter hybridization times and reduced non-specific binding. As a result, there is improved signal-to-noise ratios.

Another advantage of the present invention is that PCR/LDR allows detection of closely-clustered mutations, single-base changes, and short repeats and deletions. These are not amenable to detection by allele-specific PCR or hybridization.

In accordance with the present invention, false hybridization signals from DNA synthesis errors are avoided. Addresses can be designed so there are very large differences in hybridization T_m values to incorrect address. In contrast, the direct hybridization approaches depend on subtle differences. The present invention also eliminates problems of false data interpretation with gel electrophoresis or capillary electrophoresis resulting from either DNA synthesis errors, band broadening, or false band migration.

The use of a capture oligonucleotide to detect the presence of ligation products, eliminates the need to detect single-base differences in oligonucleotides using differential hybridization. Other existing methods in the prior art relying on allele-specific PCR, differential hybridization, or sequencing-by-hybridization methods must have hybridization conditions optimized individually for each new sequence being analyzed. When attempting to detect multiple mutations simultaneously, it becomes difficult or impossible to optimize hybridization conditions. In contrast, the present invention is a general method for high specificity detection of correct signal, independent of the target sequence, and under uniform hybridization conditions. The present invention yields a flexible method for discriminating between different oligonucleotide sequences with significantly greater fidelity than by any methods currently available within the prior art.

The array of the present invention will be universal, making it useful for detection of cancer mutations, inherited (germline) mutations, and infectious diseases. Further benefit is obtained from being able to reuse the array, lowering the cost per sample.

The present invention also affords great flexibility in the synthesis of oligonucleotides and their attachment to solid supports. Oligonucleotides can be synthesized off of the solid support and then attached to unique surfaces on the support. Segments of multimers of oligonucleotides, which do not require intermediate backbone protection (e.g., PNA), can be synthesized and linked onto to the solid support. Added benefit is achieved by being able to integrate these synthetic approaches with design of the capture oligonucleotide addresses. Such production of solid supports is amenable to automated manufacture, obviating the need for human intervention and resulting contamination concerns.

An important advantage of the array of the present invention is the ability to reuse it with the previously attached capture oligonucleotides. In order to prepare the solid support for such reuse, the captured oligonucleotides must be removed without removing the linking components connecting the captured oligonucleotides to the solid support. A variety of procedures can be used to achieve this objective. For example, the solid support can be treated in distilled water at 95-100°C, subjected to 0.01 N NaOH at room temperature, contacted with 50% dimethylformamide at 90-95°C, or treated with 50% formamide at 90-95°C. Generally, this procedure can be used to remove captured

disuccinimidyl adipate ester was applied. After a total reaction time of 1 hour, the support was washed with anhydrous DMF and dried at room temperature in a vacuum desiccator.

In case the functional group is a carboxyl group, the solid support can be reacted with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride ("EDC"). Frank, et al., "Simultaneous Multiple Peptide Synthesis Under Continuous Flow Conditions on Cellulose Paper Discs as Segmental Solid Support," Tetrahedron, 44:6031-6040 (1988), which is hereby incorporated by reference. Prior to this reaction, the surface of the solid support was protonated by a brief treatment with 0.1 N HCl. Using the above described prefabricated mask, small amounts (0.2 to 1.0 µl) of a fresh solution containing 1 M EDC (Sigma, St. Louis, MO), 1 mM of 5' amino-modified oligonucleotide and 20 mM KH_2PO_4, pH = 8.3, was manually applied to the solid support. The reaction was allowed to proceed for 1 hour, after which the support was washed with distilled water and dried at room temperature in a vacuum desiccator.

D. *Coupling of amino-functionalized capture oligonucleotides to the preactivated solid support*

For supports other than EDC-activated solid supports, small amounts (0.2 to 1.0 µl) of 1 nmol/µl 5' amino-modified oligonucleotides (i.e. the sequences in Table 2) in 20 mM KH_2PO_4, pH 8.3, were manually applied to the activated support, again using the prefabricated mask described above. The reaction was allowed to proceed for 1 hour at room temperature.

E. *Quenching of remaining reactive groups on the solid support*

In order to prevent the reaction products from being nonspecifically captured on the solid support in a capture probe-independent way, it may be necessary to quench any remaining reactive groups on the surface of the solid support after capture of the complementary oligonucleotide probes. Hereto, the support was incubated for 5 min at room temperature in 0.1 N sodium hydroxide. Alternatively, quenching can be performed in 0.2 M lysine, pH = 9.0. After quenching, the support was washed with 0.1 N sodium phosphate buffer, pH 7.2, to neutralize the surface of the support. After a final wash in distilled water the support was dried and stored at room temperature in a vacuum desiccator.

Example 2 - Design of the Assay System

A semi-automated custom-designed assay system was made for testing hybridizations and subsequent washings of captured oligonucleotide probe-capture oligonucleotide hybrids in a high-throughput format using the GeneAmp *In Situ* PCR System 1000™ (Perkin Elmer, Applied Biosystems Division, Foster City, CA) (G.J.